

REDUCTIVE AMINATION OF 2, 2'-METHYLENEBISCYCLOHEXANONE AND ITS ANALOGS WITH POTASSIUM BOROHYDRIDE AND AMMONIA (OR AMINES)

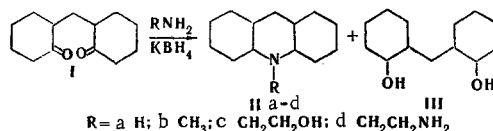
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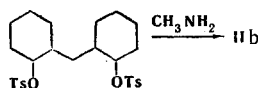
Treatment of 2, 2'-methylenebiscyclohexanone and its analogs with potassium borohydride and ammonia or amines gives perhydroacridines. The reaction is stereospecific.

1, 5-Diketones such as 2, 2'-methylenebiscyclohexanone (I) are usually converted into perhydroacridines (II) by reductive amination of the diketone with ammonia and formic acid or formamide [1, 2]. We have replaced the formic acid used as reducing agent by potassium borohydride. Reduction occurred under mild conditions, and was stereospecific.

It has been shown previously [3] that addition of I to a mixture of KBH_4 and ammonia afforded 80% of β -perhydroacridine (IIa). If the pure threo isomer of I is used, other stereoisomers of IIa are not formed. Further, if the mixture of threo and erythro isomers usually obtained is used in the synthesis, a mixture of α and β isomers of IIa is obtained in the same total yield. It follows in particular that when this method of reductive amination is used, the asymmetric atoms in I are unaffected.



From the threo-(I) KBH_4 and primary amines, we obtained N-substituted perhydroacridines. When methylamine was used, N-methylperhydroacridine (IIb) was formed. Its structure was confirmed by independent synthesis from the tosylate of trans-anti-trans-methylenebiscyclohexanol and methylamine:



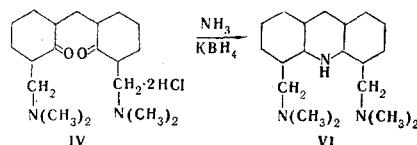
With ethanolamine, N-hydroxyethylperhydroacridine (IIc) was obtained. It was also obtained from β -(IIa) and ethylene oxide. Finally, ethylenediamine afforded N-aminoethylperhydroacridine (IId), the structure of which was confirmed by the formation of an azomethine on treatment with p-dimethylaminobenzaldehyde. In all the cases mentioned, only one of the possible stereoisomers of II was isolated from the reaction mixture.

In addition to the reductive amination of I, partial reduction to the diol III occurred, two stereoisomers of which were isolated from the reaction mixture. Treatment of I with potassium borohydride and dimethylamine gave an almost quantitative yield of III, no reductive amination product being formed.

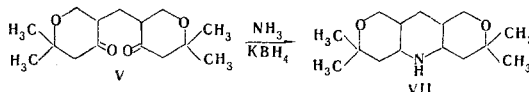
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From the diketone IV, ammonia and KBH_4 , we obtained 4,5-bis(dimethylaminomethyl)perhydroacridine (VI). In the IR spectrum of VI, stretching of the N-H bond appeared at 3300 cm^{-1} , and the $(\text{CH}_3)_2\text{N}$ group absorbed at 2820 , 2770 , and 2720 cm^{-1} .



The diketone V was converted similarly into 3,3,6,6-tetramethyl-2,7-dioxaperhydroacridine (VII), the structure of which was confirmed by its IR spectrum (the methyl and methylene groups appeared at 2960 , 2930 , 2870 , and 2480 cm^{-1} , and characteristic geminal methyl group doublet occurred at 1380 cm^{-1} . Hydroxyl and carbonyl absorptions were absent).



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EXPERIMENTAL †

Diketones IV and V were obtained according to [5] and [6], and were made available to the authors. IR spectra were taken on a UR-10 spectrometer, in CCl_4 . The products were characterized by chromatography on alumina in the systems: hexane:ethyl acetate (8:1), chloroform:ethyl acetate (4:1), and ethyl acetate.

Method of Reductive Amination. To a solution of 0.05 mole of KBH_4 and 0.5 mole of the amine (or ammonia) in 25 ml of water and 20 ml of alcohol was added during half an hour, dropwise with stirring, a solution of 0.05 mole of the diketone in 40 ml of alcohol (the diketone IV was added as an aqueous solution). The temperature of the mixture was kept at $30\text{--}35^\circ$ by water cooling. After the diketone had been added, the mixture was stirred for half an hour, then acidified with conc. HCl , and neutral material was extracted with ether. The aqueous layer was basified, the bases extracted with ether, and the ether solution was dried over magnesium sulfate. The residue after removal of the ether was recrystallized (for IIa-d) or purified by chromatography on alumina, the mixture being eluted with light petroleum-benzene (30:1), and redistilled (for VI), or (for VII), converted into the hydrochloride followed by decomposition of the latter to give the pure base. Data on the reaction products are given in Table 1.

The extract containing neutral materials obtained from I was dried over magnesium sulfate, the ether was removed, and the residue was recrystallized from alcohol to give trans-anti-trans-methylenebis-cyclohexanol, mp $151\text{--}152^\circ$ (lit. [4], mp 151°). The mother liquors were evaporated, and the residue triturated with ethyl acetate to give crystals which were recrystallized repeatedly from benzene-light petroleum. There was obtained cis-anti-cis-methylenebis-cyclohexanol, mp 125° (lit. [4], mp 128°).

N-Methylperhydroacridine (IIb). This was obtained by method [7]. 2.6 g of the ditosylate of trans-anti-trans-methylenebis-cyclohexanol (obtained from the diol, mp 124° from alcohol. Found: S 12.3, 12.2%. $\text{C}_{27}\text{H}_{36}\text{O}_6\text{S}_2$. Calculated: S 12.3%), 0.5 g of methylamine and 2.5 g of dry dioxane were heated in a sealed ampule for 3 h at 100° . The mixture was filtered, and the filtrate was basified and extracted with ether to give 1 g of IIb, which was converted to the picrate, mp $191\text{--}192^\circ$. A mixed mp with the picrate of IIb obtained by reductive amination gave no depression.

N-Hydroxyethylperhydroacridine (IIc). Through a solution of 0.02 mole of IIa in 20 ml of 75% alcohol was passed for 1 h 30 min a slow stream of ethylene oxide. After one day, the solvent was removed, and the residue was recrystallized from light petroleum. Mp $113\text{--}114^\circ$, undepressed on admixture with a sample of IIc obtained by reductive amination.

† Some of the syntheses were carried out by V. A. Fishuk.

TABLE 1. Substituted Perhydroacridines and Their Derivatives

Compound	mp, °C (solvent)	Molecular formula	Found, %			Calculated, %			Yield, %
			C	H	N	C	H	N	
IIb	63—64(light petroleum)	C ₁₄ H ₂₅ N	81,0	12,3	6,7	81,1	12,1	6,8	40
Picrate IIb	191—192(alcobol)	C ₁₄ H ₂₅ N · C ₆ H ₃ N ₃ O ₇	—	—	13,1	—	—	12,8	—
IIc	113,5—114(light petroleum)	C ₁₅ H ₂₇ NO	76,3	11,5	6,1	75,9	11,5	5,9	25
Benzoyl derivative	72,5—74 (alcobol)	C ₂₂ H ₃₁ NO	76,9	9,3	—	77,4	9,2	—	—
IIc	79—81(ethyl acetate)	C ₁₅ H ₂₈ N ₂	76,0	11,8	11,9	76,2	11,9	11,9	40
II d	101(alcobol)	C ₂₄ H ₃₇ N ₃	78,1	10,3	11,4	78,4	10,2	11,5	—
Azomethine IId with p-dimethyl-aminobenzaldehyde									
VI	*	C ₁₉ H ₃₇ N ₃	74,3	12,0	13,7	74,3	12,2	13,5	78
Picrate VI	182,5—183,5 (dioxane)	C ₁₉ H ₃₇ N ₃ · C ₆ H ₃ N ₃ O ₇	—	—	15,9	—	—	15,7	—
VII	84,5—85,5 (sublimed at 0,01 mm)	C ₁₅ H ₂₇ NO ₂	71,0	10,8	5,5	71,1	10,7	5,5	30
VII · HCl †	273 (alcobol)	C ₁₅ H ₂₇ NO ₂ · HCl	62,3	9,9	—	62,2	9,7	—	—

*Bp 118—120° (1 mm), n_D²⁰ 1.4888.

† Found: Cl 12,1%. Calculated: Cl 12,2%.

LITERATURE CITED

1. M. N. Tilichenko and V. I. Vysotskii, DAN, 119, 1162 (1958).
2. J. Colonge, I. Dreax, and H. Delplace, Bull. Soc. Chim. France, 447 (1957).
3. V. I. Vysotskii, ZhOrKh, 4, 1494 (1968).
4. A. Palsky, I. Huet, and I. Dreux, Bull. Soc. Chim. France, 4277 (1967).
5. M. N. Tilichenko and G. V. Pavel, ZhOrKh, 1, 1992 (1965).
6. M. N. Tilichenko, Izv. Vusov., Ser. Khim., 4, 96 (1961).
7. D. D. Reynolds and W. Kenyon, J. Am. Chem. Soc., 72, 1597 (1950).